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Review

Clarification of the circulatory patho-physiology of anaesthesia – Implications for high-risk surgical patients

Christopher B. Wolff [a,*], David W. Green [b]

[a] Clinical Research Centre, William Harvey Research Institute, Barts and The London Hospital Medical and Dental School, Queen Mary College, Charterhouse Square, London EC1M 6BQ, UK
[b] Anaesthetics Department, King's College Hospital NHS Foundation Trust and King's College School of Medicine and Dentistry, London SE5 9RS, UK

HIGHLIGHTS

- The article clarifies the adverse effects of anaesthesia on circulatory physiology.
- It outlines how increased venous capacity lowers CO and MAP and impairs tissue DO_2 regulation.
- Pre-emptive use of venoconstrictor and/or appropriate fluid infusion improves DO_2.
- Understanding the glycocalyx improves rational administration of fluid.
- Restorative action during anaesthesia prevents development of oxygen debt.

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ABSTRACT

The paper examines the effects of anaesthesia on circulatory physiology and their implications regarding improvement in perioperative anaesthetic management. Changes to current anaesthetic practice, recommended recently, such as the use of flow monitoring in high risk patients, are already beginning to have an impact in reducing complications but not mortality [1]. Better understanding of the patho-physiology should help improve management even further. Analysis of selected individual clinical trials has been used to illustrate particular areas of patho-physiology and how changes in practice have improved outcome. There is physiological support for the importance of achieving an appropriate rate of oxygen delivery (DO_2), particularly following induction of anaesthesia. It is suggested that ensuring adequate DO_2 during anaesthesia will avoid development of oxygen debt and hence obviate the need to induce a high, compensatory, DO_2 in the post-operative period. In contrast to the usual assumptions underlying strategies requiring a global increase in blood flow [1] by a stroke volume near maximization strategy, blood flow control actually resides entirely at the tissues not at the heart. This is important as the starting point for understanding failed circulatory control as indicated by ‘volume dependency’. Local adjustments in blood flow at each individual organ – auto-regulation – normally ensure the appropriate local rate of oxygen supply, i.e. local DO_2. Inadequate blood volume leads to impairment of the regulation of blood flow, particularly in the individual tissues with least capable auto-regulatory capability. As demonstrated by many studies, inadequate blood flow first occurs in the gut, brain and kidney. The inadequate blood volume which occurs with induction of anaesthesia is not due to blood volume loss, but probably results from redistribution due to veno-dilation. The increase in venous capacity renders the existing blood volume inadequate to maintain venous return and pre-load. Blood volume shifted to the veins will, necessarily, also reduce the arterial volume. As a result stroke volume and cardiac output fall below normal with little or no change in peripheral resistance. The resulting pre-load dependency is often successfully treated with colloid infusion and, in some studies, ‘inotropic’ agents, particularly in the immediate post-operative phase. Treatment during the earliest stage of anaesthesia can avoid the build up of oxygen debt and may be supplemented by drugs which maintain or restore venous tone, such as phenylephrine; an alternative to volume expansion. Interpretation of circulatory patho-physiology during anaesthesia confirms the need to sustain appropriate oxygen delivery. It also supports reduction or even elimination of supplementary crystalloid maintenance infusion, supposedly to replace the

* Corresponding author.
E-mail address: chriswolff@doctors.org.uk (C.B. Wolff).

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"mythical" third space loss. As a rational evidence base for future research it should allow for further improvements in anaesthetic management.

1. Introduction

There has been a great deal of controversy recently concerning perioperative haemodynamic and fluid management, particularly of high risk surgical patients. Although blood flow monitoring is reducing complications in high risk surgical patients [1] controversies surround the amount and type of fluid and the drugs designed to increase cardiac output (CO) and oxygen delivery (DO_2). Some studies show beneficial effects while others do not. What is the explanation for this disparity?

1. Optimising haemo-dynamics immediately, or very soon after the insult – e.g. from an acute reduction in MAP/CO during induction of anaesthesia or as a result of blood loss – will usually work well, in contrast to measures introduced later (e.g. starting therapy after 24 h).
2. Measures principally aimed at sustaining blood pressure (MAP) may fail to maintain tissue need for oxygen, unless DO_2 (and hence CO) are taken into account.
3. Recent studies make a strong case that current routine crystalloid maintenance regimens result in a gross excess of tissue fluid and sodium ion load and may well be a confounder for so called goal directed therapy; the protocol aimed at treating pre-load dependency.

In this paper, results are presented from a highly specific selection of clinical trials and experimental results, to illustrate perioperative mechanisms which interfere with circulatory delivery of oxygen, and illustrate ways these can be countered. Optimum management ensures sustained adequacy of oxygen delivery. Suggested therapeutic manoeuvres simplify management, relating it to the need for an adequate, but not excessive rate of oxygen supply to the tissues (DO_2) and emphasise the need to obtain pre-induction SV, CO, MAP and DO_2 reference values in elective patients and maintain them intraoperatively. This strategy may result in an improvement in outcome [2].

2. Evidence from specific trials and experimentation

2.1. An intra-operative study – Noblett et al. (2006) [3]

The study of Noblett et al. [3] demonstrates that correction of pre-load dependency (volume responsiveness) during the earliest stages of anaesthesia, can improve outcome compared with similar colloid volume given later. The patients underwent elective colorectal resection; standard volatile-based general anaesthesia was used for all patients. The control group received peri-operative fluid at the discretion of the anaesthetist in contrast to the 'intervention' (or protocol) group who received colloid boluses throughout the operative period, prompted by Doppler assessment suggesting preload responsiveness. The colloid for the intervention group was predominantly given in the earliest stages of the operation, whereas a similar total colloid volume, given to the control group, was predominantly administered during the later stages. Cardiac index (CI) was consistently higher in the intervention group compared to the control patients (Fig. 1).

Outcomes were much improved in the intervention group including; a shorter hospital stay (7 versus 9 days), reduced morbidity (2% versus 15% major complications in the control group) and significantly lower interleukin (IL) 6 values. The intervention group patients were also able to take food earlier than the control patients (2 versus 4 days). Early and effective compensation for preload dependency therefore appears to have been responsible for the improvements.

The reason behind the insufficient circulatory volume in anaesthesia is not immediately obvious since, the fluid responsive state is frequently found as early as the immediate post induction period prior to any fluid loss. There is evidence that fluid responsiveness is due to an increase in venous capacity as a result of reduced sympathetic activity. The relaxation of venous wall smooth muscle tone [4], means that the original, unchanged, blood volume is low relative to the new higher venous capacity. Hence, administration of early colloid fills the new extra capacity.

2.2. Evidence for venous relaxation and its effect on cardiac output

Evidence for venous relaxation comes from a series of experiments with dogs, where nine had complete sympathetic blockade from spinal anaesthesia [5]. The immediate result was a fall in mean arterial blood pressure to about 45 mm Hg. Normal pressure was restored by an infusion of noradrenalin (nor-epinephrine – 0.0052 mg kg^{-1} min^{-1}). The return to normal was a result of restoration of venous wall tone since, *in vitro* experimentation using rings of venous tissue has shown that nor-adrenaline causes venous wall constriction [6].

Consistent with the idea that induction of anaesthesia does not change the blood volume, but increases the capacity of the venous

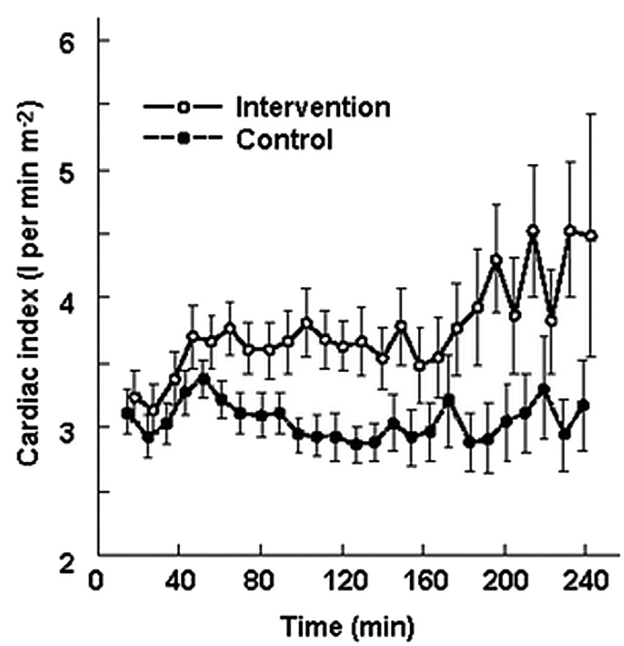

Fig. 1. Cardiac index measured at 10-min intervals during surgery, timed from immediately post-induction of anaesthesia. Values are mean (±s.d.). Noblett et al. [3] (With permission from John Wiley and Sons, publishers of the British Journal of Surgery).

system [7], is the tendency for venous inflow to the heart to oscillate to a greater extent than normal following induction and at other times where there is pre-load responsiveness. This variability is indicated by high stroke volume and/or pulse pressure variation (SVV & PPV). Excess venous capacity leads to a decrease in venous return during lung inflation and an increase in venous return as the thoracic cage relaxes during expiration. High PPV and SVV are good indicators of inadequate blood volume and thus pre-load responsiveness [8,9]

Although there is no net volume deficit following induction the increased capacity of the venous system is the basis for the reduced SV, CO and MAP. For any given inflow to the venous system, the larger venous pathway will result in a delay in the arrival of blood at the heart with a reduction in preload and cardiac output (CO). Furthermore, pooling of blood in the veins reduces arterial and capillary capacity, with immediate reduction in mean arterial pressure. The fall in SV and MAP are well illustrated by results from the study of Purushothaman et al. [10] in Fig. 2. The fall in MAP and SV on anaesthetic induction are clearly seen relative to the pre-induction values. There was little change in SVR despite the increasing depth of anaesthesia. Hence, most of the fall in MAP was a result of the lowered SV and CO. In addition, the patients with high SVV following induction had the biggest fall in SV and CO; i.e. high SVV indicated profound venodilation. Although fluids (in particular colloid) may be used to restore venous capacitance, preload, SV and CO this might better be corrected by venoconstriction.

The illustration (Fig. 2) also emphasises the reason why MAP is lowered; it is principally from reduced SV and CO, not a reduction in SVR. If the fall in MAP was due predominantly to a fall in SVR then CO would be maintained or even increased. The effects on CO and MAP of changes in venous capacity have been discussed in more detail by Guyton et al. [11] Changes in the bispectral index (BIS™, Covidien, USA) were used to assess the depth of anaesthesia; its use and validity will be discussed later.

The CO fall, for the patients' measurements illustrated in Fig. 2 was, on average, 33% (±14% SD) contributing 82% to the average fall in MAP (40% ± 12% SD). As mentioned above (see Figure text) venodilation due to propofol increases venous capacity and thus decreases venous return and preload. This fall in CO on induction of anaesthesia with propofol and etomidate has been confirmed in a recent study [12].

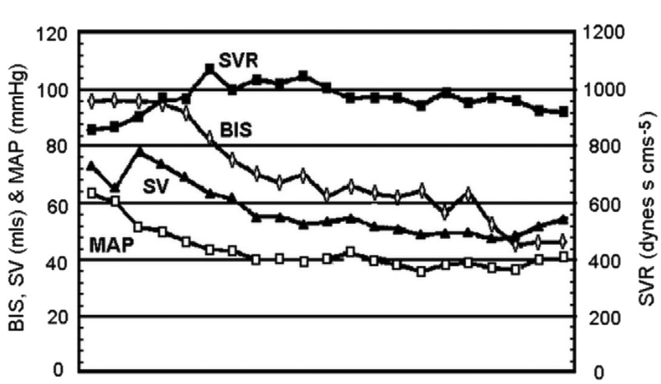

Fig. 2. Induction changes in SV, MAP, SVR and BIS (Bispectral index). BIS indicates the depth of anaesthesia. The anaesthesia was via intravenous propofol and remifentanil. This Figure was shown when the abstract – Purushothaman et al. [10] – was presented at The American Society of Anesthesiology meeting.

2.3. A post-operative study – Pearse et al. [13]

Pearse et al. [13] studied 122 high risk surgical patients in the postoperative period (62 in the protocol group, 60 in the control group). The protocol included initial post-operative correction of pre-load dependence and utilised SV responses to colloid boluses to maximize CO. Dopexamine supplementation was given subsequently to patients who failed to reach a particular DO_2 (DO_2I 600 ml min^{-1} m^{-2}). In most cases, where the DO_2 goal was not reached with supplementary colloid, it was achieved with dopexamine administration. For the control patients central venous pressure (CVP) changes were used to guide dosage of colloid. Control group patients were not given dopexamine supplementation.

Improvements, following protocol group treatment, included shorter hospital stay than for the CVP controlled group (median duration 11d versus 14d), and less complications (27 versus 41). It is likely that, with postoperative intervention, compensatory therapy (higher DO_2) was required to make up for deficiencies in DO_2 (oxygen debt) incurred during surgery.

2.4. Fluid overload as a confounder

The above two major clinical studies [3,13] support the idea that peri-operative CO measurement, utilizing appropriate volume supplementation with colloid fluids and inotropes, improve outcome. The extra aim in the postoperative study [13], to reach a particular DO_2, was based on factors to be considered later, after some observations here concerning crystalloid fluid supplementation.

Some recent studies appear to refute the claim that perioperative optimization (or 'maximisation') of SV and hence CO, with colloid and inotrope, improves outcome during and after anaesthesia. Otherwise it would be a simple matter to recommend universal implementation of the colloid fluid supplementation approach. Fluid overload has, however, been shown to be a real concern [14]. The study of Lobo et al. [15] has addressed the problem, in particular, with regard to 'maintenance' intravenous (iv) crystalloid. It is important to avoid lumping crystalloid and colloid together simply as fluid, since crystalloid adds to all compartments, colloid principally, at least initially, to the circulatory volume.

The study of Lobo et al. [15] utilized a DO_2 goal similar to that of Pearse et al. [13] above, for two groups; one with typical crystalloid 'maintenance' iv crystalloid (lactated Ringer's solution, 12 ml kg^{-1} h^{-1}), the other with a considerably lower infusion rate (4 ml kg^{-1} h^{-1}). Optimization of DO_2I was continued throughout surgery and for the following 8 h. Both groups showed a reduced incidence of complications relative to earlier studies on a similar group of patients [16]. There was, however, a significantly greater reduction in complications where maintenance crystalloid was limited (restricted group 20.0%; conventional group 41.9%). This was despite the conventional group having higher DO_2. High crystalloid infusion rates therefore appeared to confound advantages gained from the treatment of pre-load dependency.

It is possible that even better results would be obtained by avoiding continuous supplementary intra-venous crystalloid infusion altogether, except under circumstances where there have been significant, measured, excess fluid losses. Chappell et al. [17] suggest that most, so called, restrictive regimens could still result in the infusion of more crystalloid than required. This is because the fluid deficit from fasting, insensible fluid loss, evaporation during surgery was thought to be exacerbated by a loss of functional extracellular fluid, referred to as '3rd space' loss. This has now been refuted [18].

It has been shown that routine infusion of 12 ml kg^{-1} h^{-1} of Na^+ based fluid such as 0.9% NaCl or Hartmann's/Lactated Ringer's to replace the "imaginary" 3rd space loss often results in gross fluid overloading. Operative complications correlate strongly with both weight gain and excess fluid [19]. Chappell et al., 2008 [17] recommend the use of crystalloid specifically for replacement of measured losses of fluid and electrolyte, (colloid is more appropriate for intra-vascular volume expansion). The introduction of so called "restrictive" or "zero balance" intraoperative fluid administration techniques has been introduced [20], because methods used to determine the, so called, "third space loss" were flawed [21].

2.5. Crystalloid, colloid and the glycocalyx

Two major advances have clarified the understanding of fluid absorption from the capillary lumen. Firstly, measurement of interstitial tissue hydrostatic and colloid osmotic pressure led to revision and then it was found that there is a layer of tissue, the glycocalyx, constituting a previously unknown component lining the endothelium [22,23]. It was thought, originally (Starling hypothesis), that fluid passed out of capillaries over the earlier part of capillary transit, while capillary hydrostatic pressure (P_c) exceeded plasma protein osmotic pressure (π_c). Then it was thought that fluid was re-absorbed, as P_c fell below π_c. However, it is now known that outflow from capillaries is continuous, with uptake into lymphatic vessels equal to the total plasma water every 9 h. Reabsorption at the venous end only occurs transiently when there is a sudden fall in pressure. The only tissues where extra-vascular fluid moves into capillaries in a sustained manner are lymph nodes vessels, renal tubules (cortical peri-tubular capillaries and the ascending vasa recta) and, during the intestinal absorptive phase.

Understanding of glycocalyx physiology has clarified the calculation of the expected balance between intra-vascular and interstitial hydrostatic and colloid osmotic pressures which had predicted too great an outflow. It also transpired that the sub-glycocalyx space colloid osmotic pressure (π_g) rather than the interstitial colloid osmotic pressure (π_i) was the major determinant of the colloid osmotic pressure gradient between the capillary lumen and the interstitial fluid.

The glycocalyx constitutes a layer which lines the whole circulatory endothelial surface. In the capillaries there are tight junctions between the endothelial cells at the base of shallow clefts between the cellular endothelial surfaces. These channels are covered by the glycocalyx forming the sub-glycocalyx spaces. Sufficient albumin is present to create the sub-glycocalyx osmotic pressure (π_g). There are widely spaced gaps in the tight junction which are entrances to tortuous pathways to the interstitial tissue space. Outflow of fluid passes through these purely under the residual hydrostatic pressure. So, the forces generating outflow are P_c, interstitial fluid pressure P_i and π_c and π_g.

The glycocalyx exhibits many important functions in addition to its partial penetration by albumin. Negative charges are responsible for an exclusion zone with central streaming of red cells and other cellular blood components [24]. It is delicate with vulnerability to damage, losing much of its bulk when there is excess volume expansion from either crystalloids or colloids. Even though crystalloid expansion is briefer the damage is done where an excess is infused over and above a blood volume already adequate or larger than normal. Colloid and crystalloid effects on blood volume, and blood pressure, were compared as pre-load prior to spinal anaesthesia for caesarean section, with a dose dependent expansion from colloid (hydroxyl-ethyl starch solution); better normalization of arterial blood pressure occurred with the higher of two concentrations of colloid [25]. Here the expansion is appropriate filling the dilated venous compartment.

The decision to use colloid for blood volume expansion in anaesthesia fulfils a need to fill the expanded venous capacity – there is no fixed blood volume. The appropriate volume of the vascular compartment is that which keeps the venous side of the circulation sufficiently stretched to avoid loss of arterial volume and hence arterial blood pressure. The circulation is then more appropriately filled than it is without the added volume. As pointed out earlier, the use of phenylephrine is probably a better way of achieving compatibility between blood volume and capacity since it acts towards restoring normal capacity by compensating for the anaesthetic derived loss of tension in the venous walls.

There are different clinical situations where it is argued that crystalloid infusion is more appropriate, especially in longer term situations, as in intensive care. The reasoning concerns the inhibition of hepatic albumin metabolism since permeable capillaries allowing extensive hepatic penetration with colloid can impair normal hepatic function and albumin production [26].

2.6. Tissue regulation of blood flow

Clinical practice has lost sight of the fact that the majority of individual tissues regulate their own blood flow; known now for around 100 years. Regulation of blood flow to individual organs and parts of those organs occurs via appropriate local adjustment of input resistance. At rest blood flow is normally sustained virtually constant in the face of wide variations in arterial blood pressure [27]. In the review of organ auto-regulatory capabilities by Green et al. [27] they quote multiple studies showing the strongest auto-regulatory capabilities are those of skeletal muscle and heart whereas the weakest capabilities are those of intestine (gut) and liver (splanchnic areas). Brain and kidney show intermediate auto-regulatory capability. Skin does not auto-regulate its blood flow (the priority is thermal) and for bone blood flow the total and its regulation are uncertain. The great majority of blood flow is therefore regulated by the tissues. Auto-regulation has been shown to be independent of innervation [5,11]. Since blood flow is determined at the tissues venous return, total tissue blood flow, determines the input to the heart (pre-load). Starling showed that the heart will always put out what it receives, over a wide range of inflow, contractility and heart rate [28,29]. As pointed out in the recent paper by Bidd et al. [30] "the heart is the servant of the tissues".

The tissue priority, for the majority of tissues, is to receive oxygen at the appropriate rate [31], normally achieved remarkably successfully. For each tissue type the DO_2 required bears a specific relation to the rate of oxygen consumption. This will have been an evolutionary priority, since an adequate DO_2 ensures sufficiently rapid blood flow for all other metabolites [11].

2.7. Arterial and venous blood volumes

There is a big difference between the volume of blood in the venous and arterial compartments (see upper panel of Fig. 3). The rest of the blood volume (around 20%) resides in the pulmonary circulation. If we assume a total blood volume of 5 L, 3 L (60%) would reside in the venous side but only 600 ml (12%) in the arteries. Even a modest increase in venous capacitance of 200 mls following induction could well result in a 1/3rd reduction (200 ml) of arterial blood volume. A fall in MAP would inevitably follow (Fig. 3, middle panel).

When the blood volume is inadequate and MAP is low, the reduced arterial and capillary volume will prevent auto-regulation working in the most vulnerable tissues, contributed to by the reduction in arterial volume. Hence, for the organs with the lowest auto-regulatory capability blood flow becomes inadequate to sustain

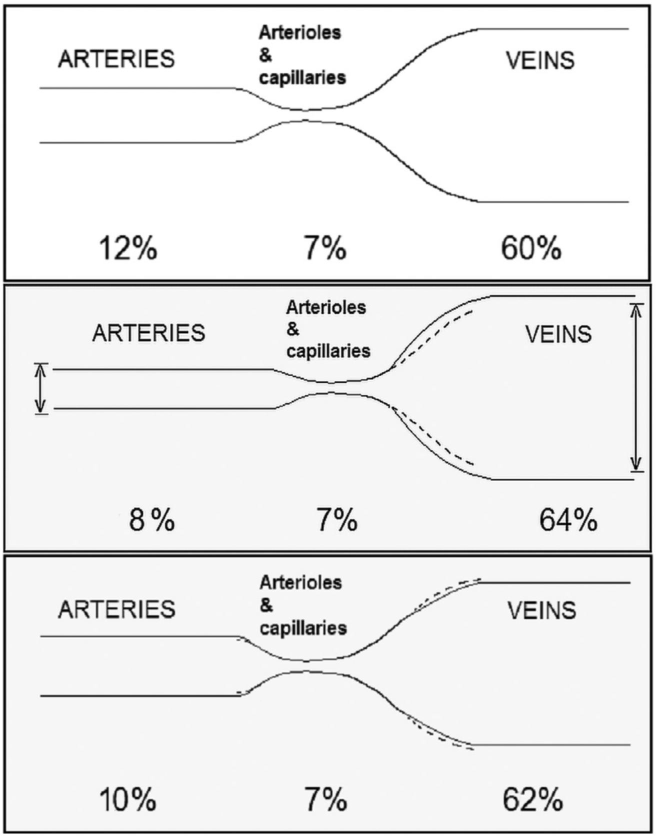

Fig. 3. The upper panel shows the normal volume relations of arteries, arterioles/capillaries and veins. The arterial volume is only one fifth of the venous volume. The middle panel represents relaxation of the veins by around 200 ml. The loss of 200 ml from the arterial compartment reduces its volume by 1/3rd. The lower panel shows the effect expected from partially re-constricting the veins with phenylephrine, say by 100 ml. The increase in arterial volume will improve the pressure. (Around 20% of blood volume is in the pulmonary circuit.)

normal local VO_2. The reduction in blood flow to the splanchnic area, the brain and the kidneys leads to a reduced total tissue blood flow, reduced venous return, and hence reduced CO, SV and DO_2.

2.8. Impaired tissue blood flow regulation

Individual studies have shown early impairment of splanchnic blood flow, cerebral blood flow and renal blood flow associated with increased pre-load (volume) responsiveness [32]. We can illustrate this in relation to the patho-physiology discussed above. Fig. 4 is a diagrammatic representation of the blood volume as a percentage of capacity, also showing schematically individual blood flows in gut, brain and kidney. The degree of excess SVV increases as the actual blood volume becomes a lower percentage of the increased vascular capacity (principally venous). Blood flows, in these vulnerable organs, are affected successively as the venous capacity increases so that available blood volume as a percentage of capacity decreases.

Impaired gastro-intestinal perfusion is recognized as an early consequence of inadequate blood volume. Improvement in outcome has been shown to result from early treatment (with colloid), based on finding gastric mucosal ischaemia, by means of gastric tonometry [32,33]. Early studies were reviewed by Lebuffe et al. [34] and confirmed the crucial role of gastro-intestinal ischaemia in the instigation of severe side effects, including multiple organ dysfunction (MODS) and sepsis. The reduction in blood flow, with progressive volume responsiveness, probably occurs first in the gut blood supply, but the precise organ sequence, for brain and kidney, requires investigation and may vary. Cerebral oxygenation is monitored with near infra-red spectroscopy (NIRS) in some centres, also acting as an early warning of inadequate blood volume [35–38]. Adequate cerebral oxygenation helps sustain good cerebral function [35] and is also a good indicator of adequate systemic oxygenation [38]. Renal near infra-red spectroscopy (NIRS) has been used extensively in paediatric surgery [39] but has found limited applicability for adult monitoring, thought to be due to a limited depth of tissue penetration by NIR photons.

Haemorrhage gives rise to a reduced blood volume. The extreme sensitivity of the gut blood flow to an inadequate blood volume is demonstrated by the animal study of Guzman et al. [40] Fig. 5 illustrates the early impairment of blood supply to the ileal mucosa during progressive haemorrhage. In this experiment mucosal perfusion began to decline after the loss of two small volume increments; yet there was no obvious effect on other organs, even after considerable mucosal perfusion deficit.

The brain also suffers early ischaemic change after haemorrhage, often with little if any indication from systemic markers. Cerebral NIRS detects the ischaemia as a fall in cerebral oxygen saturation (rSO_2). Reduced cerebral oxygen saturation has been found to be an early warning of haemorrhage, in the absence of pre-load dependency, Hence, NIRS reduction in rSO_2 may be an

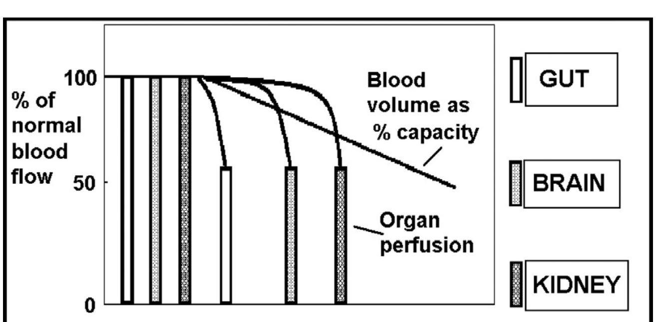

Fig. 4. The vertical bars represent the percentage of normal blood flow in three major organ systems with moderate or low auto-regulatory power (gut, brain and kidney). The full length bars represent normal blood flows. The sloping line depicts the percentage of increased blood volume capacity filled by the actual blood volume. With the decline in percent capacity (and rise in SVV) gut, brain and kidney develop inadequate blood flows (shorter bars) due to impaired auto-regulation.

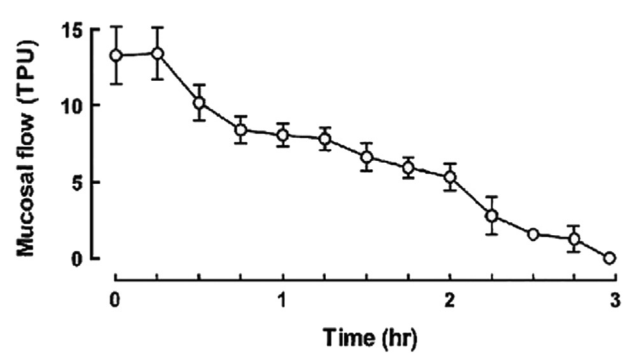

Fig. 5. Ileal mucosal blood flow in dogs subject to controlled haemorrhage – 5 ml kg^{-1} every 15 min. The fall in blood flow after the first increment occurred with very little overall haemodynamic change. Intestinal mucosal auto-regulation is far less robust than for heart, skeletal muscle and even the brain. After Guzman et al. [40] (With permission from The American Physiological Society, APS). Key: TPU – Tissue Perfusion Units.

early indicator of the need for blood transfusion and haemostasis [36,41].

2.9. Auto-regulation of oxygen delivery

Recent work has confirmed and extended that of Guyton et al. [11] that the supply of oxygen to the tissues in the arterial blood (DO_2) is normally well sustained in the face of low arterial oxygen content (due to either hypoxia or anaemia) by augmentation of local blood flow. In subjects with a normal blood volume, DO_2 is sustained at the normal level in hypoxia and anaemia unless arterial oxygen content (CaO_2) drops too low. Below critical levels, local blood flow progressively fails to compensate and DO_2 starts to decline.

With pre-load dependency the impaired auto-regulation and reduced blood flows in gut, brain and renal vessels are accompanied, initially, by increased oxygen extraction (the same rate of oxygen consumption from a smaller rate of delivery). This results in localised tissue ischaemia with adverse consequences despite continuation of a normal overall VO_2. It is only when the oxygen supply is grossly reduced that the rate of oxygen consumption falls – with generation of an oxygen debt. The ischaemic range is still important in that function is impaired.

Measures to improve and sustain adequate blood flow are therefore fundamental to the maintenance of adequate DO_2. The idea that DO_2 optimization may have advantages over and above simple correction of volume responsiveness with colloid infusion requires further clarification.

2.10. Oxygen delivery, tissue ischaemia and oxygen debt

The normal rate of oxygen delivery in fit young men at rest (non-indexed) is around 1200 ml min^{-1}). The indexed value is around 666 ml min^{-1} m^{-2} [42,43]. Shoemaker et al. [44,45] showed, retrospectively, that high risk surgical patients with post-operative DO_2I values lower than around 600 ml min^{-1} m^{-2} had high morbidity and mortality rates. With low CO and in some cases, low oxygen consumption (VO_2), lower DO_2 correlated with poor outcome more closely than with any other, of the many comprehensively recorded, clinical measures. Patients with DO_2I values at or above 600 ml min^{-1} m^{-2} in the 8 h post-operative period had very low morbidity. This value corresponds with a non-indexed DO_2 value around 1080 ml min^{-1}, lower than for fit young men at rest, but probably generous even for the most normal hospitalized subjects.

In study by Lugo et al. [46] on 20 high risk surgical patients, mean oxygen delivery index (DO_2I) pre-operatively was 460 ml min^{-1} m^{-2} (calculated from values in a table (not the value 560 given in the text).

In a study monitoring DO_2, CO and VO_2 before, during and following operation Shoemaker et al. [47] calculated a higher mean pre-operative DO_2 index of 586 (± 29) ml min^{-1} m^{-2} for those who survived without complications. For patients who survived but had complications mean DO_2I was 503 ± 28 ml min^{-1} m^{-2} and was a little lower still, at 485 ± 27 ml min^{-1} m^{-2}, for non-survivors. The study also showed a clear relationship between the number of complications and peri-operative oxygen debt. Oxygen debt was obtained by making an estimate of the required VO_2 from the patient's own resting pre-operative control values and calculating the VO_2 deficit (oxygen debt) from the measured VO_2 minus a 15% lower VO_2 need (as a result of the effects of anaesthesia on VO_2). Fig. 6 shows results from an illustrative case. The deficit during a 3 h operation showed considerable worsening as it progressed post-operatively.

Shoemaker et al. [48] undertook a prospective study comparing protocol patients versus control patients on standard care. The protocol included colloid supplementation and dobutamine and/or dopamine, to achieve DO_2I values up to or above 600 ml min^{-1} m^{-2} during the immediate post-operative period. Morbidity and mortality were considerably reduced relative to control patients (in whom DO_2I was significantly lower).

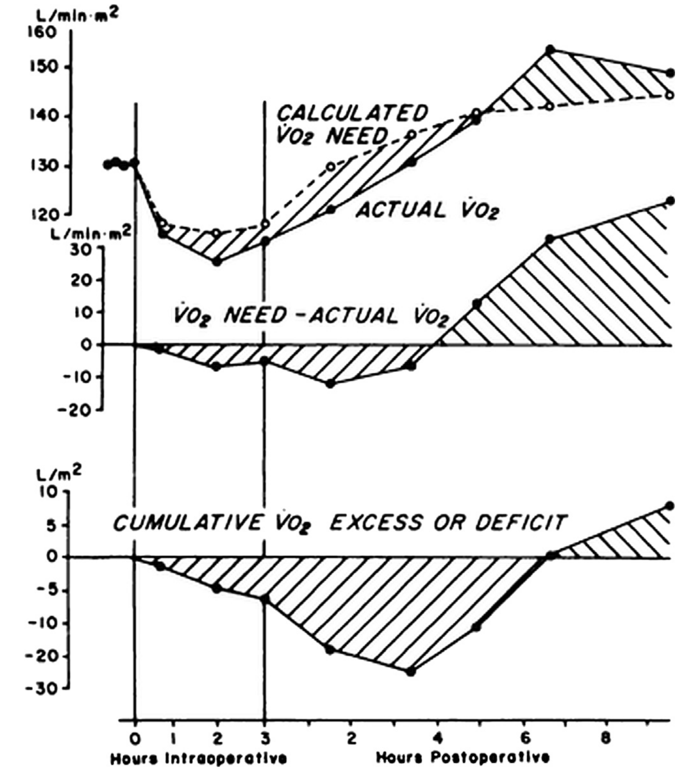

Fig. 6. Results from one patient [(Shoemaker et al.; 1992, [47]. Upper section, serial measurements of VO_2 (solid line) and estimated VO_2 requirements (dashed lines) in an illustrative case. Middle section, VO_2 deficit measured as difference between actual measured VO_2 and VO_2 need. Lower section, cumulative VO_2 deficit (below) or excess (above) zero line. (Reproduced with permission from the American College of Chest Physicians).

The pre-induction DO_2 values were lower than those needed post-operatively; suggesting the oxygen debt was created intra-operatively. Hence, a post-operatively increased DO_2 is required to correct for the oxygen debt generated during the operation.

The relationship between low DO_2 and poor outcomes receives strong support from a study on dogs [49]. Deaths which occurred in response to bleeding were specifically and uniquely related to oxygen debt – the cumulative difference between normal oxygen consumption (VO_2) and the declining rate of oxygen consumption during progressive haemorrhage.

The many studies of Shoemaker's group led to development of goal directed therapy. The aim was to sustain a post-operative DO_2I of around 600 ml min^{-1}, with colloid infusion. Dopamine, dobutamine or dopexamine were added where colloid alone was insufficient. Appreciable increases in CI of the protocol patients were achieved postoperatively. This work has been supported by others [50,51] and includes the above post-operative study of Pearse et al. [13] where the protocol group achieved an average DO_2 of 600 ml min^{-1} m^{-2} or more. The DO_2I profile for the Pearse et al. [13] study is shown in Fig. 7.

2.11. Filling with colloid alone

The reduction of complications from the simple colloid filling undertaken, during the earliest stages of the operative procedure,

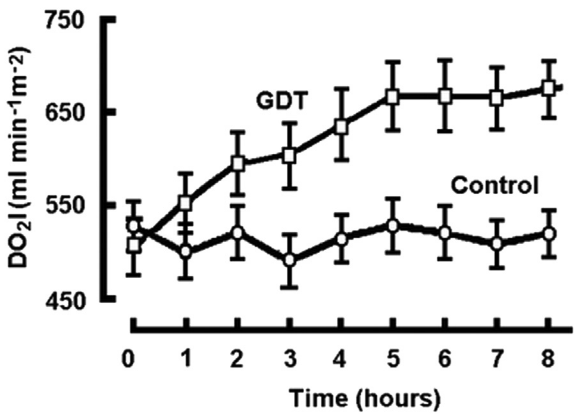

Fig. 7. Oxygen delivery index for goal-directed therapy and control groups during the 8-h post-operative study period. Results are means ± SEM. DO_2I, oxygen delivery index; GDT, goal-directed therapy. [(Pearse et al., 2005, ([13])], (Permission from Critical Care publisher BioMed Central).

by Noblett et al. [3], were likely to have been related to an early increase in DO_2, though values from their study are not available. The study of Wakeling et al. [52] also utilized colloid infusion intra-operatively to maximize Doppler assessed SV and achieved increased CO values. Improved outcomes relative to control patients (central venous pressure – CVP -guided) were accompanied by an increase in DO_2 despite the dilution effect of colloid infusion. These studies support intra-operative action to fill the available volume where it has increased from venous relaxation.

2.12. O_2 and auto-regulation

The fact that extra DO_2 post-operatively may counter deficiency incurred during operation, and thereby improve outcome, emphasises the likely value of maintaining pre-induction DO_2 intra-operatively in elective patients.

The importance of maintaining DO_2 is related to the absence of an oxygen store. The rate of oxygen delivery must keep pace with the rate of tissue oxygen consumption. There is less reserve for oxygen than for the supply of any other nutrient or for removal of any waste product. Oxygen is limited in its rate of carriage whereas other substances are not. Guyton, Jones and Coleman [11] point out that the maximum reserve for oxygen is a factor of 3 (utilization of 2/3rds, assuming capability for maximal oxygen extraction).

The reserve for oxygen is even more limited than would be the case if it were possible to extract 2/3rds of that normally carried in arterial blood. Even modest increases in oxygen extraction mean the tissue is, at least moderately, ischaemic.

The normal rates of DO_2 to different tissues are precisely related to the individual VO_2 and it is the appropriate ratio which is sustained when blood volume is normal [31]

2.13. Pre-induction measurement and early infusion of veno-constrictor

Measurements made prior to induction are likely to represent adequate CO and DO_2 since they give a measure of the normal state in the elective patient. Values of SV, CO and DO_2 made prior to induction can therefore function as reference values during the operative period. The aim emerging from the analysis in this paper is to sustain DO_2 close to the reference value. It has been found that a small dose of phenylephrine (0.25–0.5 $\mu g\ kg^{-1}\ min^{-1}$), started prior to induction, can reduce the fall in SV which commonly follows induction. A typical fall in SV (and MAP) at induction (illustrated earlier in Fig. 2) is shown in Fig. 8 (left hand panel, no phenylephrine). The patient, whose result is shown in the right hand panel, was started on a phenylephrine infusion prior to induction. The percentage fall in SV and MAP is less marked. The values, from pre-to post-induction, were SV 145 ml–100 ml (a fall of 31%) for no drug and 145 ml–120 ml (a fall of 17%) following induction on phenylephrine.

This manoeuvre, thought to partially reverse the venous relaxation from propofol, [7] reduces the fall in CO and DO_2. It appears to reduce the subsequent incidence of episodes of volume responsiveness and hence reduces the need for further fluid infusion.

The work of Sharpey-Shafer, in the early 1960s (1961 and 1963) [53,54] on 'venous tone' is interesting. The studies showed increased values, relative to normal, in normal subjects on standing and in anaemia and congestive cardiac failure. Furthermore, increases were observed following administration of adrenaline and noradrenaline. Hence, the clinical responses to nor-adrenaline may be from effects on venous constriction (with an increase in venous tone), rather than their supposed inotropic effect on the heart. It may be time to revisit measurement of venous tone to augment available data on cardiovascular function.

3. Conclusions

By understanding the circulatory response to anaesthesia and relating it to the patho-physiology, it may be possible to further improve outcomes by sustaining pre-induction DO_2 and limiting oxygen debt intraoperatively, rather than trying to repay debt by

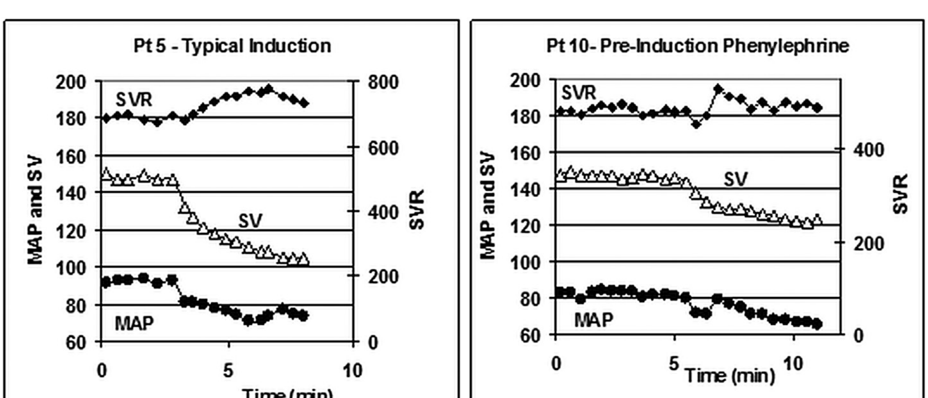

Fig. 8. The figure shows the situation at induction of anaesthesia in two patients. On the left the patient's induction proceeded without phenylephrine pre-medication. On the right phenylephrine had been administered, as an infusion from 5 min pre-induction (15 $\mu g\ min^{-1}$), and the fall in stroke volume (SV) lessened. Note systemic vascular resistance (SVR) did not fall (often assumed to be the reason for lowering of blood pressure). Green DW (unpublished).

maximising DO_2 post-operatively in an HDU or ICU environment. It is probably not necessary to maximise SV but rather to sustain CO and DO_2 at, or close to, the pre-induction (reference) level.

Extra benefits may also be derived from the ability to monitor depth of anaesthesia and cerebral and tissue oxygenation [30]. Excess depth of anaesthesia (DOA) is recognised as one of the causes of circulatory depression with low CO and MAP. DOA monitors are now recommended in patients who are at greatest risk of cerebro-vascular depression, due to inadvertent excess DOA (e.g. the elderly) [55].

Recent NICE guidelines [56] recognise the need for blood flow monitoring during surgery, particularly in patients considered at high risk for complications. It has been estimated that universal adoption of blood flow monitoring with appropriate responses would produce very large reductions in costs, complications and mortality [57]. Inclusion of further recommendations made here, and better understanding of the patho-physiology, should allow further savings in morbidity and mortality, with concurrent reduction in the expense involved in the care of high risk surgical patients.

Ethical approval

None.

Sources of funding

None.

Author contribution

Dr Wolff wrote the original draft including clinical illustrations and new analysis of the background patho-physiology.

Dr Green improved much of the text and brought further illustrative work to our notice with supportive clinical measurements and modifications brought to bear following years of practical experience in anaesthesia.

Conflict of interest

None.

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